Myelodysplastic Syndromes in Older Adults:

Diagnosis, Prognosis and Treatment

Objectives

- Understand the pathophysiology of MDS
- Become Familiar with Subtypes of MDS
- Workup Macrocytic Anemia and Diagnosis of MDS
- Prognosis
- Treatment

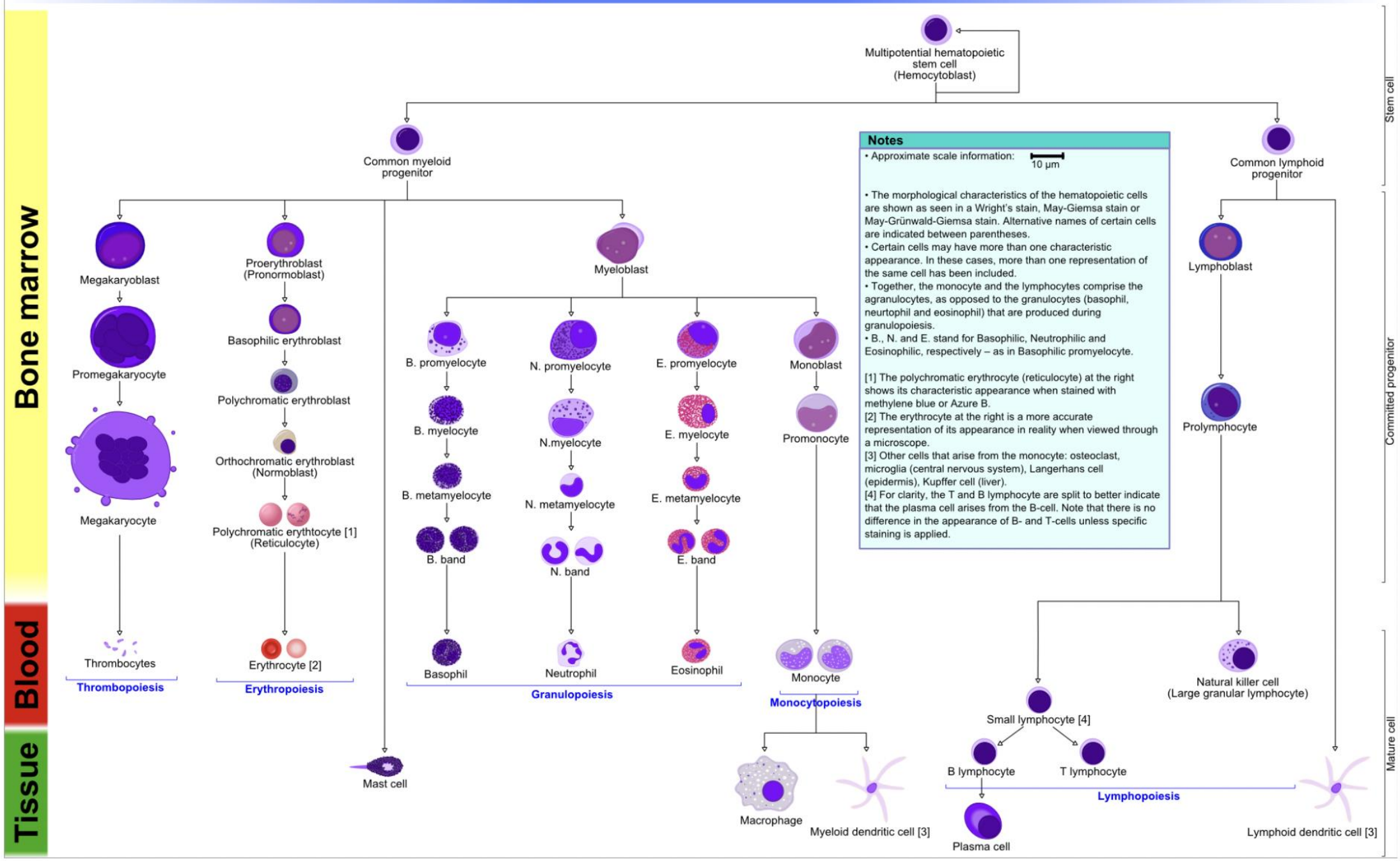
Myelodysplastic Syndromes : Brief Overview

- Ineffective hematopoiesis that affects one, two, or all three myeloid cell lines—erythrocytic, granulocytic, megakaryocytic
- Presents in older patients with pancytopenia, possible peripheral blasts and hypercellular marrow on biopsy
- MDS is a precursor of AML as it shares clinical and pathologic features
  - The major difference is MDS has a lower percentage of blasts in bone marrow (<20 %)
  - MDS will convert into AML in about 30% of patients
- The goal of treatment is to prevent progression to AML and decrease need for transfusions

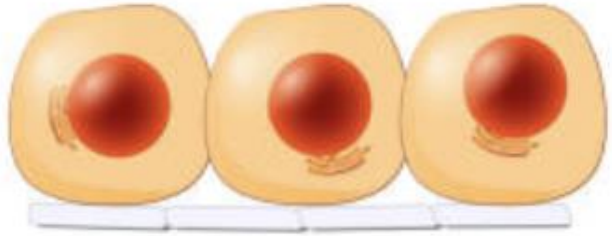
Myelo*dysplasia* → abnormal cells in the bone marrow

[1]

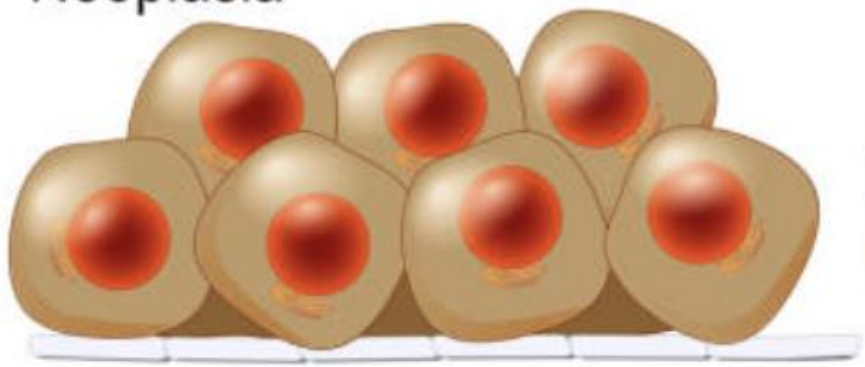
Hematopoiesis in humans



Normal cell

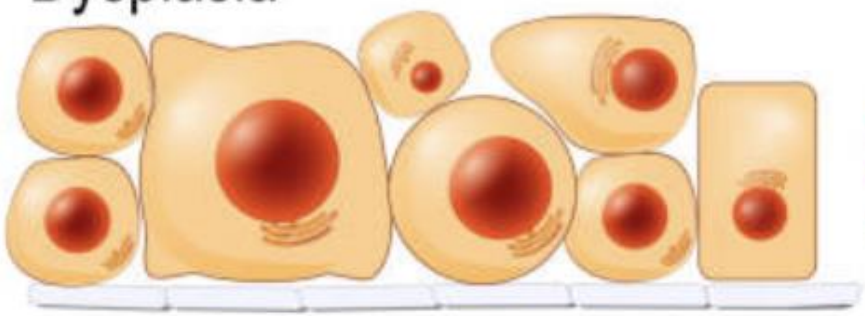


Neoplasia



Abnormal,
and excessive
growth of cells

Dysplasia



Abnormality
of development,
and differentiation

Causes of MDS

- De novo mutation : 90% of MDS (primary)
- Environmental Exposures: benzene, chemotherapy, radiation, tobacco use ~ 10% (secondary)
  - At risks occupations: chemical plant workers, painters, oil refinery workers, paper factory workers
- A very small proportion of patients have MDS as a result of an inherited genetic condition affecting their bone marrow, such as Fanconi anemia or Trisomy 21

[1]

MDS History

- MDS was labeled a disease in 1976
- Original scoring system was the French-American-British or FAB system
- In 1999, the World Health Organization, or WHO, published a more specific classification system to replace the FAB system. This was revised in 2008 and then 2016
- The International Prognostic Scoring System (IPSS) was implemented in 1997, which is a scoring system used to classify the risk of progression of MDS subtypes and survival
- IPSS was then revised (IPSS-R) in 2011
- MDS was not classified as neoplastic disorder until 2001

[2]

Epidemiology of MDS

- Data from the National Cancer Institute's Surveillance, Epidemiology & End Reports (SEER) shows that 86% of MDS cases are diagnosed in individuals 60 years of age or older, with the median age being 76
- SEER data also reveals that the incidence of MDS increases significantly with age, ranging from 0.7 per 100,000 population in their 30s to 36.3/100,000 after age 70
- There is a fivefold difference in risk between age 60 and ≥80 years
- Estimates in the United States are thought to be around 40,000 new cases per year
- At all ages, MDS is more common in males than in females with an incidence rate of 4.5 men vs 2.7 women per 100,000 population

[3]

2016 WHO Classification: 6 Main Types of MDS

1. MDS with single lineage dysplasia (MDS-SLD)
2. MDS with multilineage dysplasia (MDS-MLD)
3. MDS with ring sideroblasts (MDS-RS)- *SF3B1* mutation
4. MDS with excess blasts (MDS-EB)
5. MDS with isolated del(5q)
6. MDS, unclassifiable (MDS-U)- MDS cytogenetics +/- dysplasia

MDS Patient Presentation

Patients with MDS may complain of excessive fatigue, bruising, bleeding, night sweats, bone pain, fever, skin rash, undesired weight loss, and recurrent infections. Studies have identified excessive fatigue as one of the most debilitating symptoms of this disease. These symptoms usually correlate with cytopenias

OR

The development of myelodysplastic syndromes (MDS) may be preceded by a few years with an unexplained macrocytic anemia

Macrocytosis, Megalobastic Anemia and MDS - *what is happening?*

Macrocytosis has a prevalence of about 4%, estimated about 60% of patients present **without** anemia – there are no specific recommendations regarding workup in this case but it is advised to obtain LFTs, B12, TSH, reticulocyte count

- A prospective study of 300 hospitalized patients with macrocytosis (with and without anemia) showed that 100% of bone marrow disorders that explained the macrocytosis also caused anemia [12]

Megaloblastic Anemia (MBA) and Myelodysplastic Syndrome (MDS) are two separate entities in the diagnostic workup of macrocytic anemia

- MBA is a **reversible** form of ineffective hematopoiesis, typically Vitamin B12 or folate deficiency while MDS is an **irreversible** disorder of ineffective hematopoiesis

Evaluation of Macrocytic Anemia

Kaferle , Joyce, and Cheryl E. Strzoda . “Figure 3 Algorithm for the Evaluation of Macrocytic Anemia. .” *Evaluation of Macrocytosis* , American Family Physician , 1 Feb. 2009, www.aafp.org/afp/2009/0201/p203.html.

Causes of macrocytosis and macrocytic anemia

- Drugs: HIV medications, folic acid antagonists (methotrexate), 6-mercaptopurine, azathioprine, cytarabine, phenytoin/valproic acid, nitrous oxide, Bactrim, metformin, PPIs, cholestyramine
- Vitamin B12 deficiency, folate deficiency, and copper deficiency (typically occurs secondary to zinc overload)
  - - Serum folate can be misleading, you can consider red blood cell folate level
- Hypothyroidism
- Liver disease
- Hemolysis
- COPD: EPO causing excessive bone marrow turn out (macrocytosis)
- EtOH : direct toxicity on bone marrow vs. chronic EtOH use with co-existing B12/folate deficiency
- Spurious Causes: hyperglycemia and leukocytosis
  - In the lab, blood is diluted to measure the mean corpuscular volume and in the setting of hyperglycemia, the RBCs can swell, causing a false elevation in MCV
  - Increased turbidity of a sample due to leukocytosis also can cause the machine to overestimate the cell size

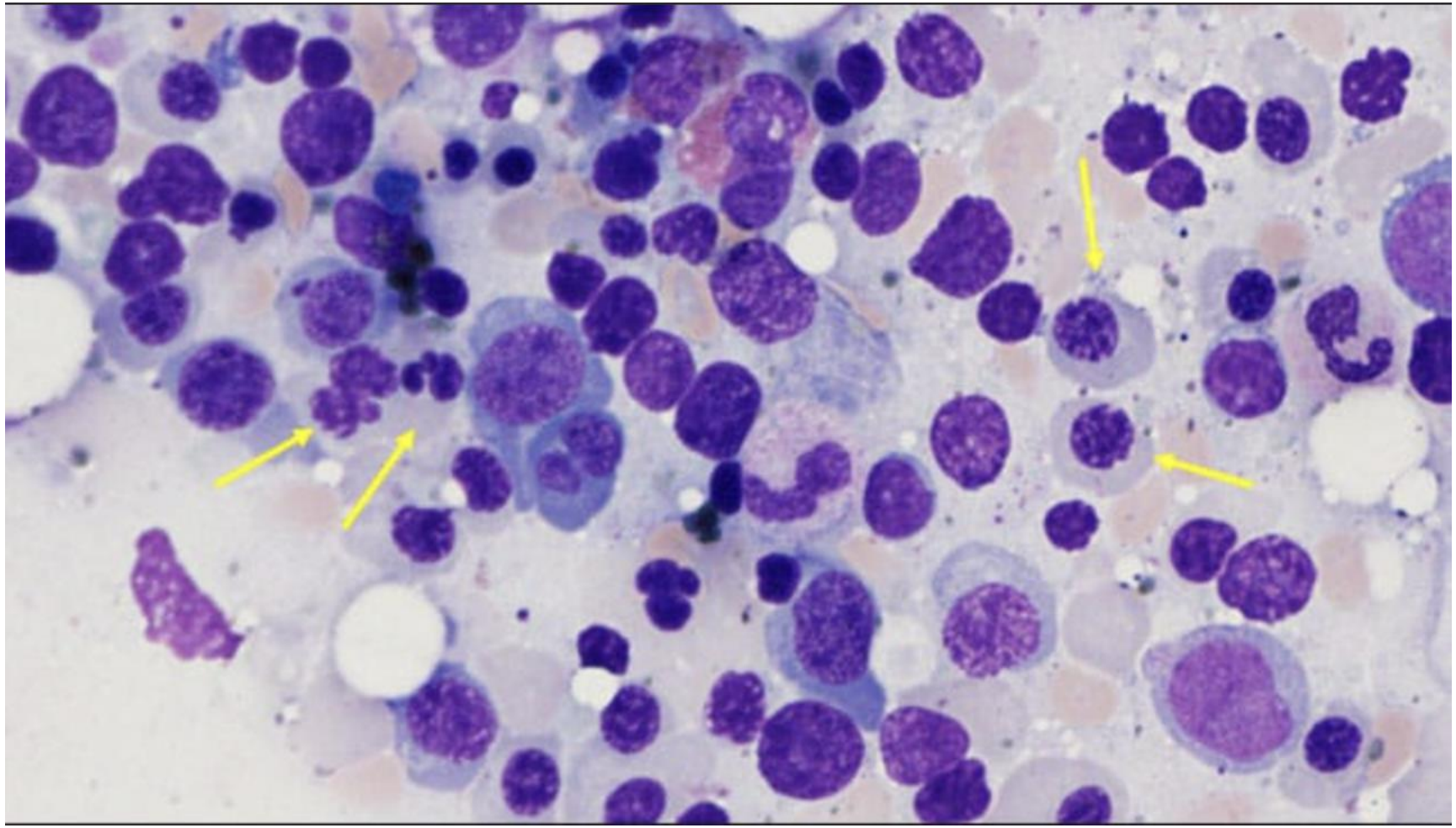
MDS Mimics
Other Causes of Cytopenias to Consider

- Heavy Metal Toxicity (lead, zinc, arsenic)
- Alcohol abuse
- HIV infection
- Aplastic anemia (remember this will have hypocellular bone marrow)
- Immune-mediated cytopenias (eg large granular lymphocyte leukemia, ITP)
- Felty Syndrome: classic triad of RA, splenomegaly, granulocytopenia
- CML
- Idiopathic cytopenia of undetermined significance (ICUS): persistent cytopenias without dysplasia
- Idiopathic dysplasia of undetermined significance (IDUS): does not meet MDS criteria

Basic Workup

- CBC with differential : most commonly macrocytic anemia (HgB < 10 g/dL, MCV>100 fl), with increased RDW (given co-existing microcytic and macrocytic cells), leukopenia specifically neutropenia (ANC <1800/uL), thrombocytopenia (plts < 100,000 /uL)
- Peripheral smear
- Reticulocyte count- usually decreased (hypercellular marrow with poor maturation)
- A normal serum B12 level may not rule out a true B12 deficiency, but normal levels of the metabolites methylmalonic acid and homocysteine essentially rule it out
- TSH to rule out hypothyroidism
- LFTs to evaluate for liver disease
- bone marrow aspirate with cytogenetic studies

Pathology

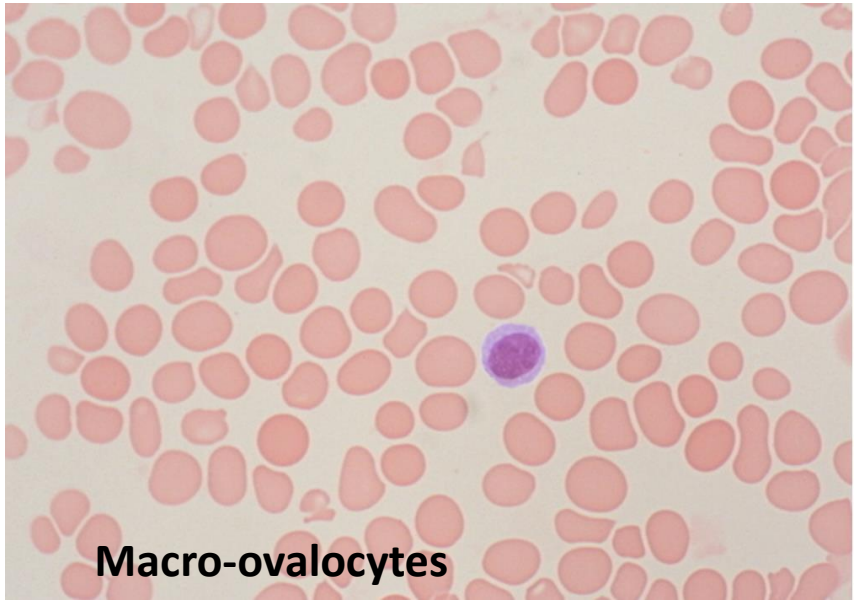


[4]

Peripheral Blood Smear Findings

- The peripheral blood count may show a single cytopenia (anemia, thrombocytopenia, or neutropenia), bicytopenia (2 deficient cell lines) or pancytopenia (3 deficient cell lines)
- Anemia varies in degree from mild to severe. It is usually macrocytic (mean cell volume of >100 fL) with red blood cells (RBCs) that are oval-shaped (macro-ovalocytes), **contain basophilic stipling**
- Neutropenia may vary from mild to severe. Morphologic abnormalities are often observed in the granulocytes. These can include bilobed nuclei (**pseudo–Pelger-Huet** abnormality) or **hypersegmented nuclei** (6-7 lobes) similar to megaloblastic diseases
- Platelet counts are decreased (rarely increased), tend to be large, immature and agranular

[1]



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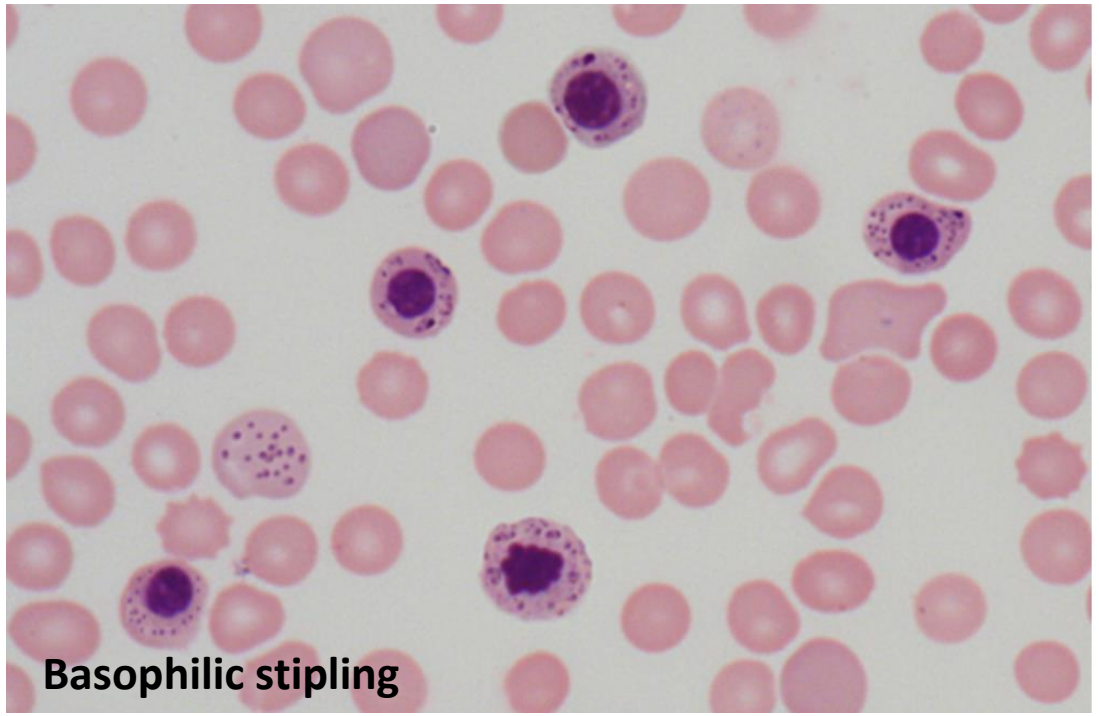

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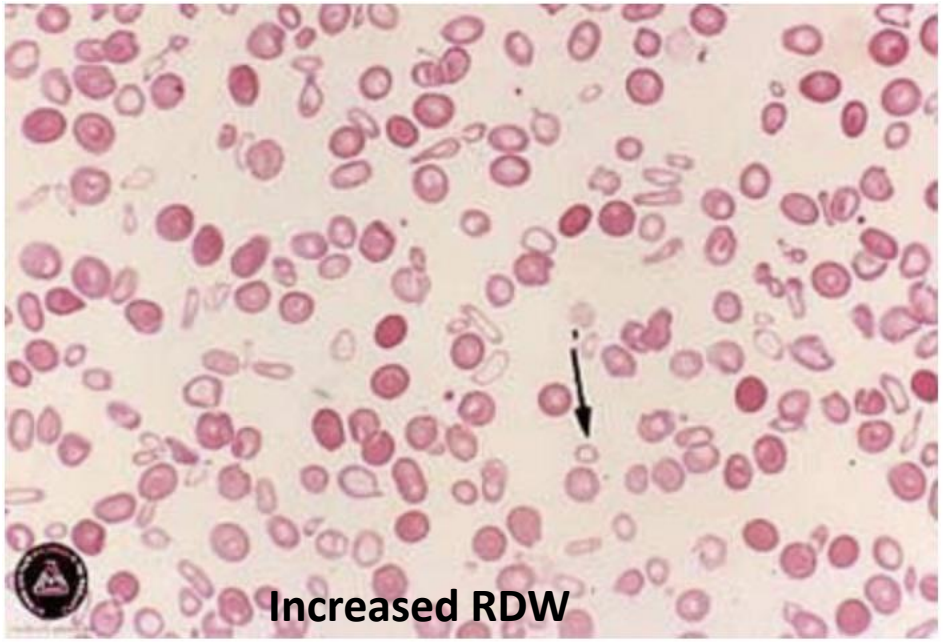

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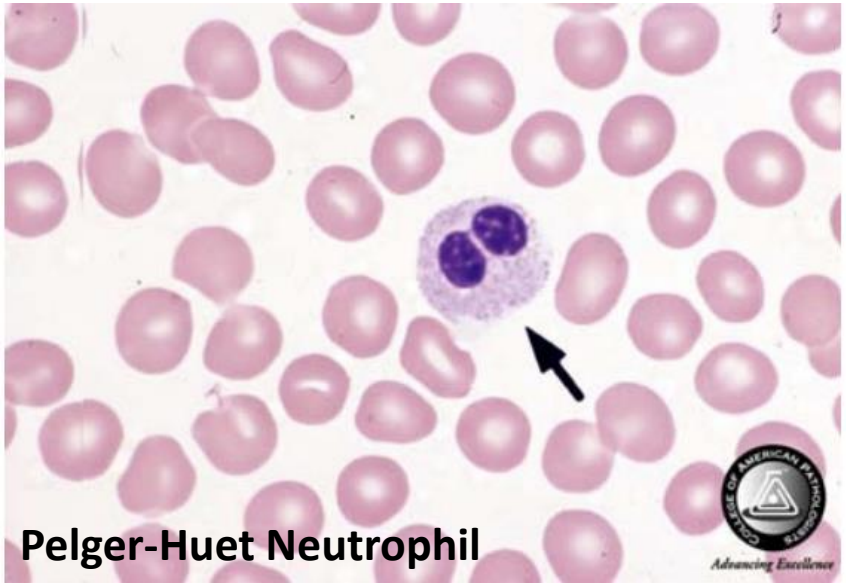
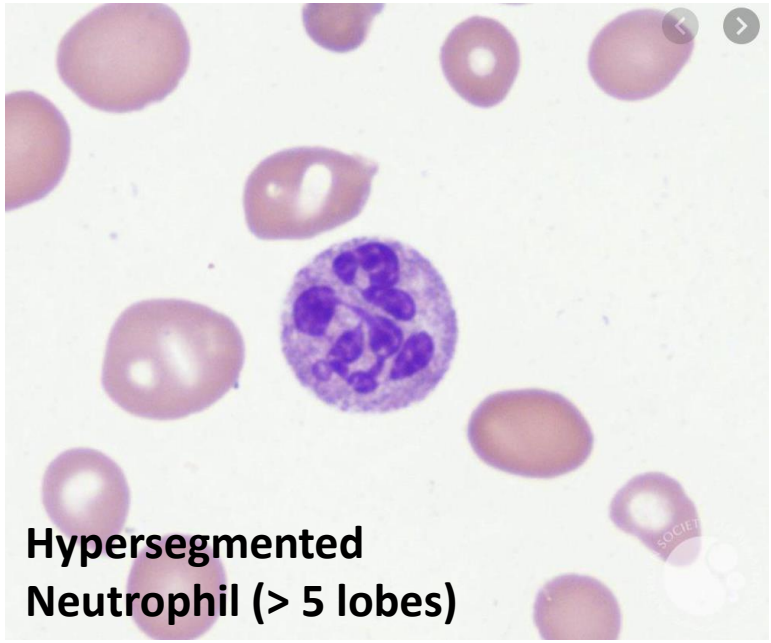
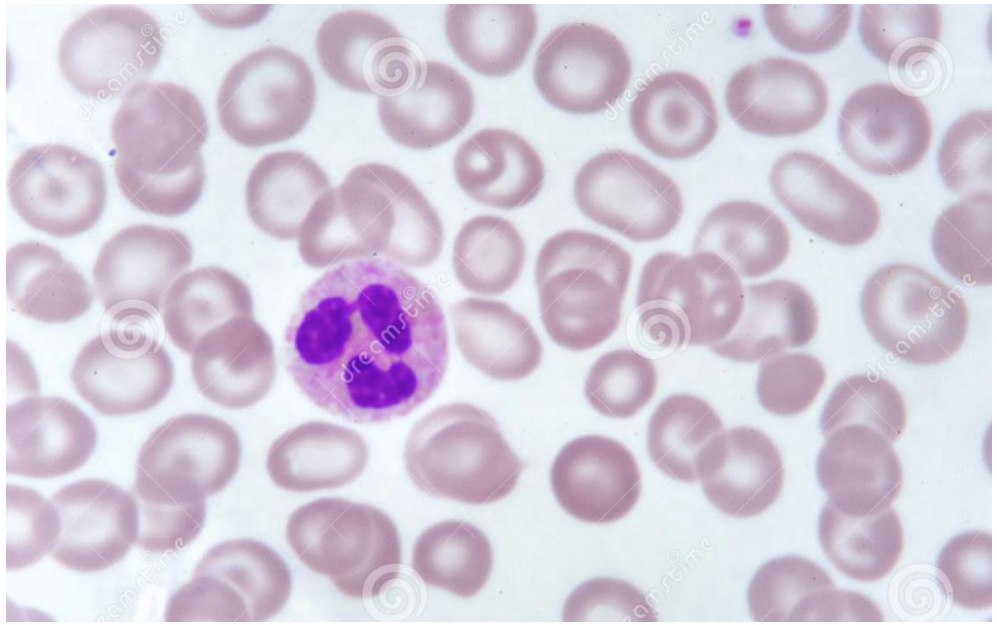


Pelger-Huet Neutrophil

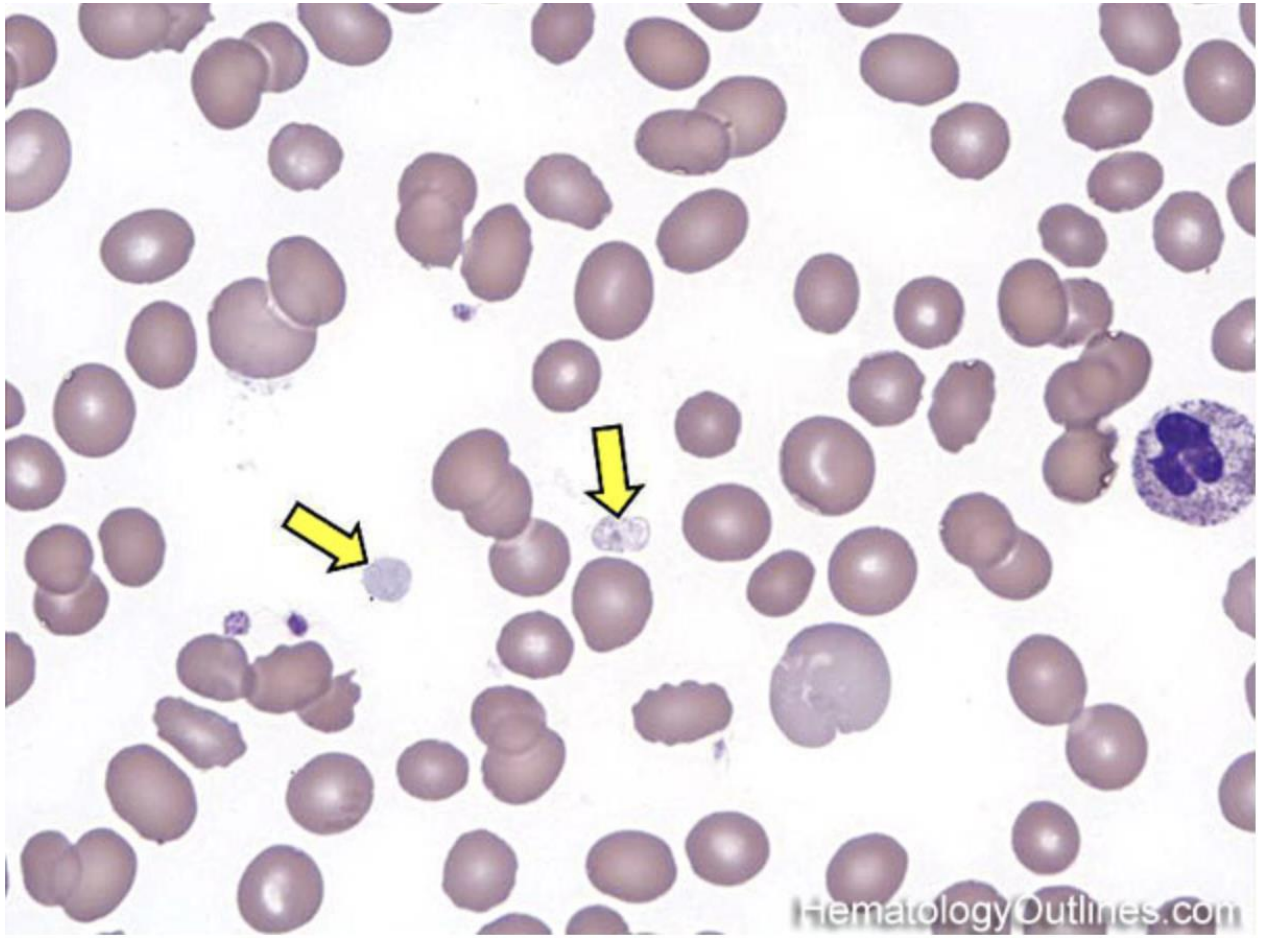


Hypersegmented Neutrophil (> 5 lobes)

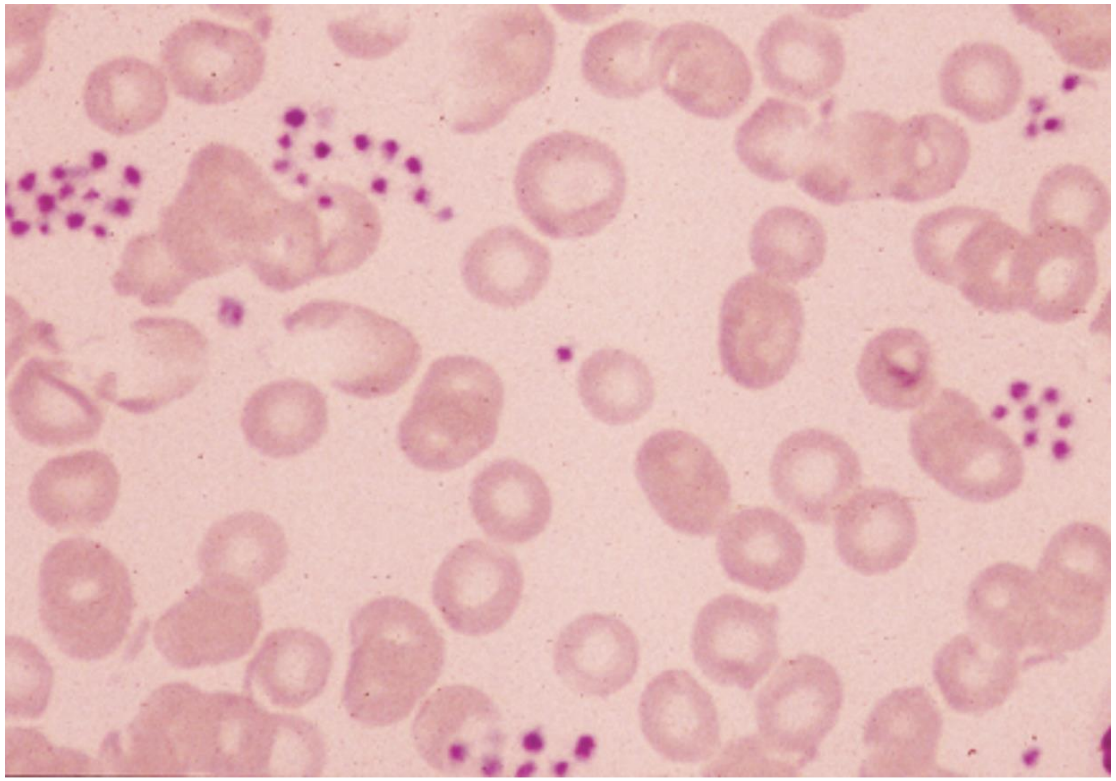


Normal Neutrophil

[6]



Large agranular platelets

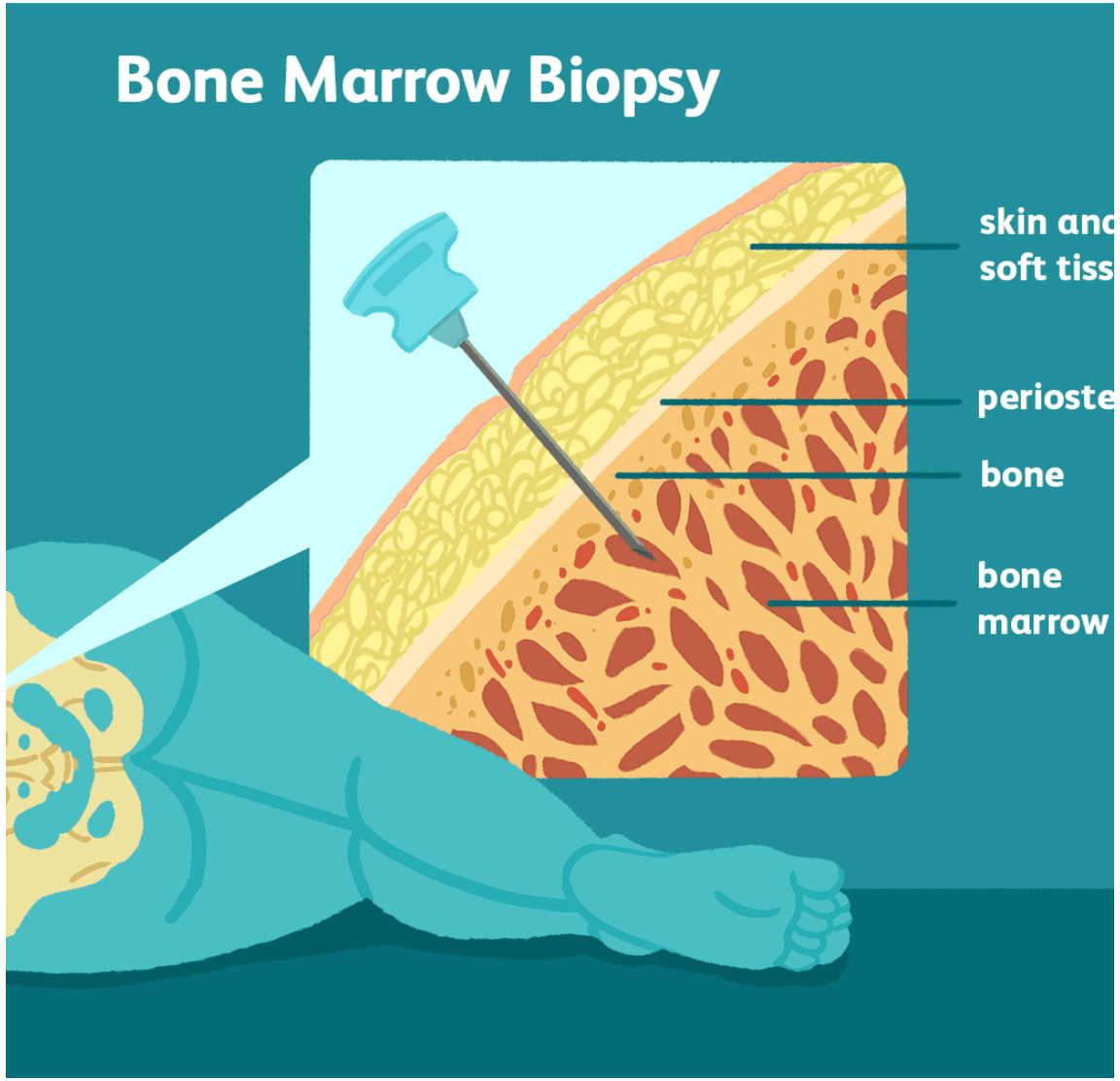


Normal platelets, clumped

Bone Marrow Biopsy

- (Myelo) Blasts < 20%
- Hypercellular Marrow
- Cytopenias
- Dysplasias > 10% of a single or multiple cell lines
- Leukoerythoblastosis (immature WBCs, immature RBCs)
- Run cytogenetics and next generation sequencing to determine the presence of gene mutations for specific MDS subtypes

[1]



Chromosomal Abnormalities

MDS-defining abnormalities

- del(5q), del (7q), del(9q), del(11q), del(13q), del(12q) del(20q), Isochromosome 17q, idic(X)(q13)
- t(11;16), t(3;21), t(1;3), t(2;11 t(6;9), t(3;3)(q21.2;q26.2), inv (3)

Gene Mutations and Next Generation Sequencing

From “Molecular Genetics in Myelodysplasia Outcomes Prognostication.” By Rifkin, Lucas H., MD, & Loo, Eric Y., MD. (2019). *Advances in Molecular Pathology, 2*(1), 35-43.

	SRSF2	5%–15%	Adverse
	U2AF1	12%–16%	Adverse
	ZRSR2	~5%	Unclear
Tumor suppressor	TP53	5%–10%	Adverse
Cohesin complex	STAG2	5%–7%	Adverse
	RAD21	~2%	Adverse
	SMC3	~2%	Adverse
DNA methylation	TET2	20%–30%	Unclear
	DNMT3A	~10%	Adverse
	IDH1/2	~5%	Unclear
Histone modification	ASXL1	15%–20%	Adverse
	EZH2	5%–10%	Adverse

Prognosis

Clinical risk is based on blood counts (degree and number of cytopenias), % of blasts in bone marrow, types of chromosomal abnormalities (karyotypes of affected cells) → International Prognostic Scoring System- Revised (IPSS-R)

30% of patients with MDS will transform into AML

Next Generation Sequencing can identify mutations that may respond to certain treatments and portend better or worse prognosis

[1]

International Prognostic Scoring System- Revised [IPSS-R]

IPSS-R Cytogenetic risk groups*,**

Cytogenetic prognostic subgroups	Cytogenetic abnormalities
Very good	-Y, del(11q)
Good	Normal, del(5q), del(12p), del(20q), double including del(5q)
Intermediate	del(7q), +8, +19, i(17q), any other single or double independent clones
Poor	-7, inv(3)/t(3q)/del(3q), double including -7/del(7q), Complex: 3 abnormalities
Very poor	Complex: >3 abnormalities

*Greenberg, Tuechler, Schanz et al, Revised International Prognostic Scoring System (IPSS-R) for Myelodysplastic Syndrome, Blood 120: 2454, 2012.

**Schanz J et al, J Clin Oncology 2012; 30:820

International Prognostic Scoring System- Revised [IPSS-R]

IPSS-R Prognostic Score Values*

Prognostic variable	0	0.5	1	1.5	2	3	4
Cytogenetics	Very Good		Good		Intermediate	Poor	Very Poor
BM Blast %	<=2		>2-<5%		5-10%	>10%	
Hemoglobin	=>10		8-<10	<8			
Platelets	=>100	50-<100	<50				
ANC	=>0.8	<0.8					

*Greenberg, Tuechler, Schanz et al, Revised International Prognostic Scoring System (IPSS-R) for Myelodysplastic Syndrome, Blood 120: 2454, 2012.

International Prognostic Scoring System- Revised [IPSS-R]

IPSS-R Prognostic Risk Categories/Scores*

RISK CATEGORY	RISK SCORE
Very Low	<=1.5
Low	>1.5 - 3
Intermediate	>3 - 4.5
High	>4.5 - 6
Very High	>6

*Greenberg, Tuechler, Schanz et al, Revised International Prognostic Scoring System (IPSS-R) for Myelodysplastic Syndrome, Blood 120: 2454, 2012.

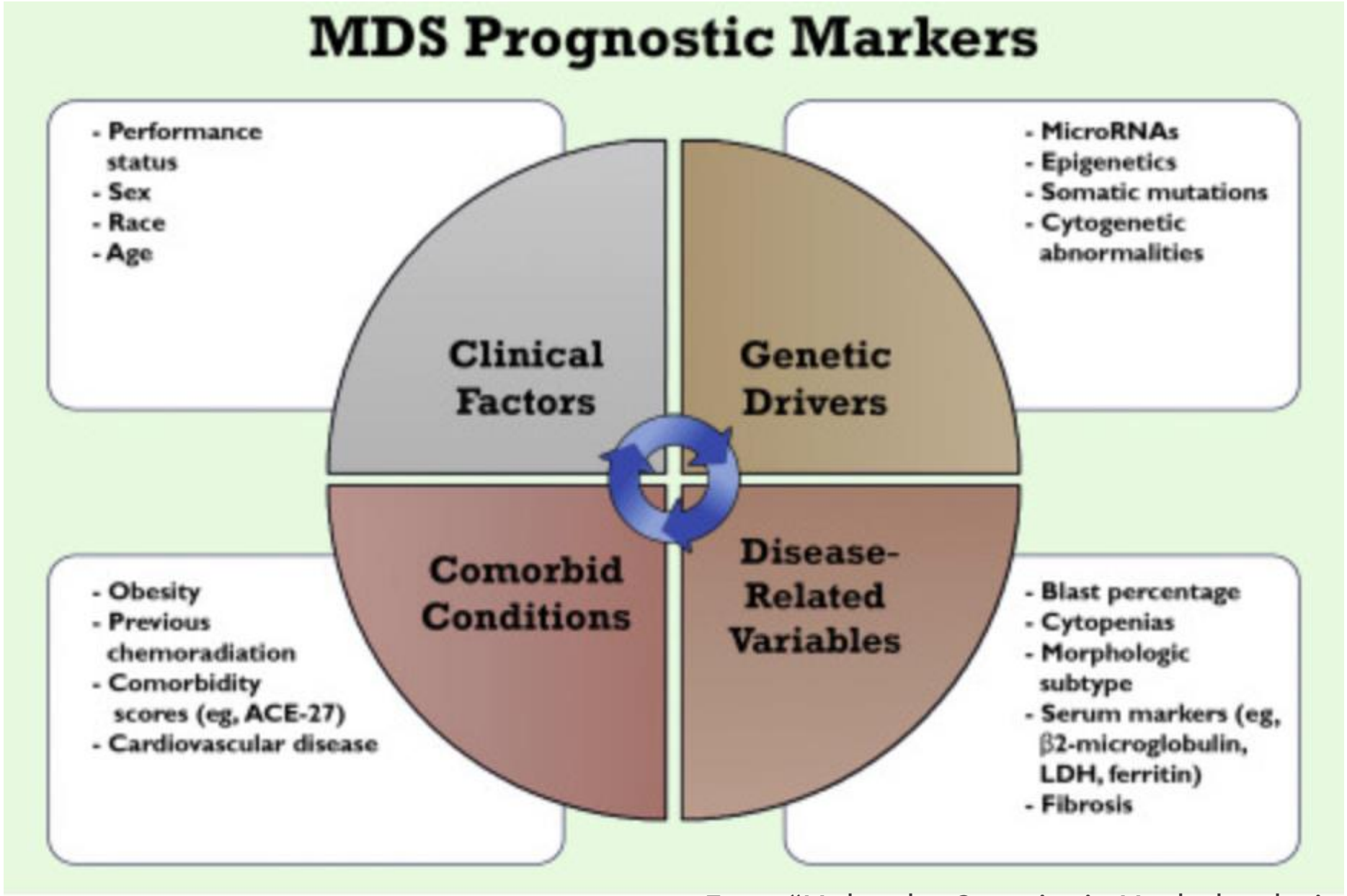
International Prognostic Scoring System- Revised [IPSS-R]

IPSS-R: Prognostic Risk Category Clinical Outcomes*

	No. pts	Very Low	Low	Intermediate	High	Very High
Patients (%)	7012	19%	38%	20%	13%	10%
Survival***		8.8	5.3	3.0	1.6	0.8
Median Survival (yrs)						
AML/25%***,^		NR	10.8	3.2	1.4	0.7

Median Time to transformation to AML (yrs)

*Greenberg, Tuechler, Schanz et al, Revised International Prognostic Scoring System (IPSS-R) for Myelodysplastic Syndrome, Blood 120: 2454, 2012.



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MDS/MPN Overlap Syndromes

- Have both dysplastic and proliferative features and prognosis is poor compared to a diagnosis of just Myelodysplastic Syndromes or Myeloproliferative Neoplasms
  - MDS/MPN with ringed sideroblasts and thrombocytosis
  - Chronic Myelomonocytic Leukemia
  - Atypical Chronic Myeloid Leukemia

[1]

Treatment

- MDS is only curable with allogeneic stem cell transplant
- long term survival is not improved by treating *asymptomatic* low risk MDS patients
- The focus for the treatment of older patients with MDS is therefore not curative, but rather alleviation of symptoms, improvement in quality of life, maintenance or improvement of functional status, and continued independent living

Indications for Treatment

- Symptomatic anemia
- Symptomatic thrombocytopenia
- Severe Neutropenia (ANC < 500/uL) or symptomatic with recurrent infections
    - Prophylactic use of G-CSF or GM-CSF will increase ANC but does not decrease infection risk or increase survival in MDS patients

- High Risk MDS Patients [8]

Treatment of Low Risk Patients

The goal of therapy is not complete remission but to treat symptoms and improve quality of life

Supportive therapies: repeated blood transfusions + iron chelating agents, plt infusions, and antibiotics for recurrent infections

- Symptomatic Anemia with HgB < 10 g/dL or transfusion dependent
  - EPO level ≤ 500 mU/ mL → give lowest effective dose of EPO, HgB remain ≤ 11.5 to decrease risk of thrombosis
  - EPO level > 500 mU/ mL → consider targeted therapy
- Thrombocytopenia (plts < 20K/uL or < 50K/uL with bleeding
  - Thrombopoietin receptor agonists: romiplostim (Nplate®), eltrombopag (PROMACTA®), avatrombopag (Doptelet®)
- Multiple Cytopenias or Neutropenia: consider targeted therapy

[8]

Specialized Therapy

Luspatercept (REBLOZYL®):

- approved in April 2020 for low risk-MDS to intermediate risk with ring sideroblasts
- SQ injection given once every 21 days, can be continued forever if effective
- median increase of 3g/dL in HgB over 3 months
- 1/3 patients becoming transfusion independent

Lenalidomide (Revlimid®)

- used for treatment of MDS with cytogenetics consistent with deletion 5q MDS (low risk)
- effective at reducing RBC transfusion dependence
- 67% patients remained transfusion independent for 8 weeks (occurred after 3 months of treatment)
- ~50% patients transfusion independent after 1 year
- Median increase in hemoglobin was 5.4 g/dL (1.1-11.4) in patients achieving transfusion independence
- 10mg tablet taken daily for 21 days of a 28 day cycles
- Grade 3 or 4 hematologic toxicity was seen in 80% of patients enrolled in the study, predominately thrombocytopenia and neutropenia [16]

[10]

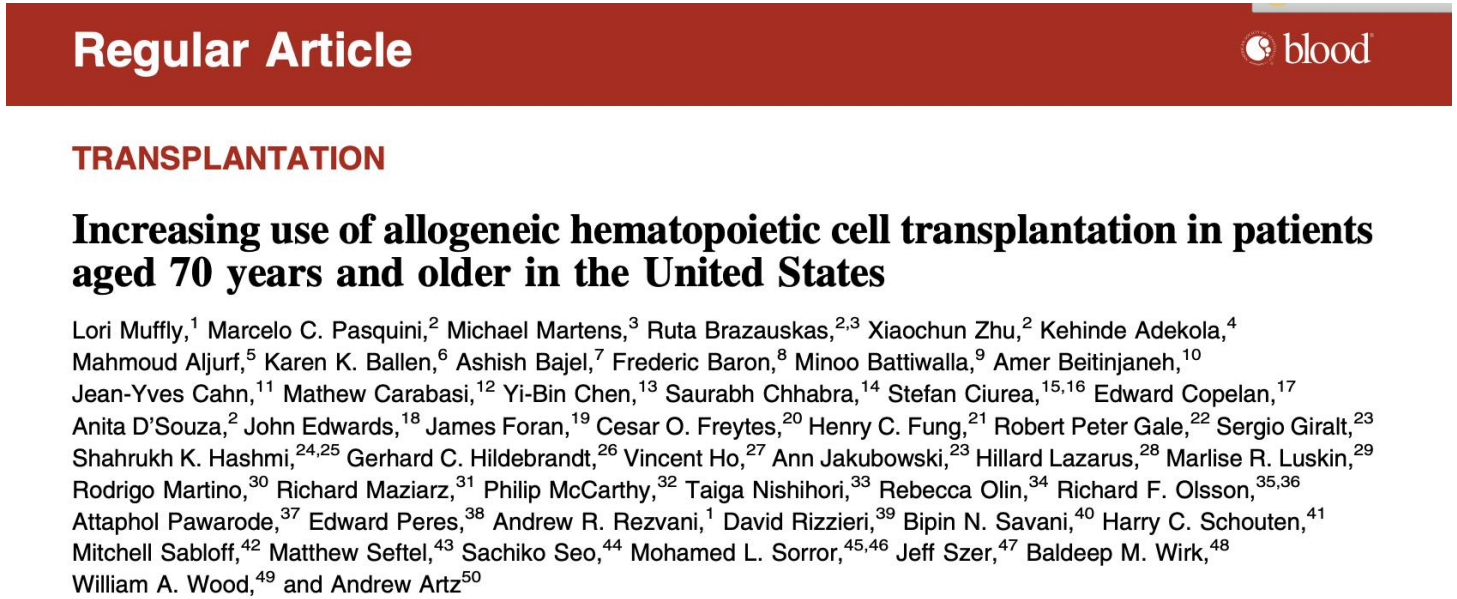
Immunosuppressive Agents

Anti-thymocyte Globulin (ATG) + cyclosporine :

~29% response rate in low risk -MDS, possibly more effective with certain MDS mutation subtypes

Stem Cell Transplant (HCT)

In recent years, the development of reduced-intensity conditioning (RIC) and nonmyeloablative (NMA) regimens, coupled with more accurate HLA typing methods has broadened the application of HCT to include older adults.



Regular Article

blood

TRANSPLANTATION

Increasing use of allogeneic hematopoietic cell transplantation in patients aged 70 years and older in the United States

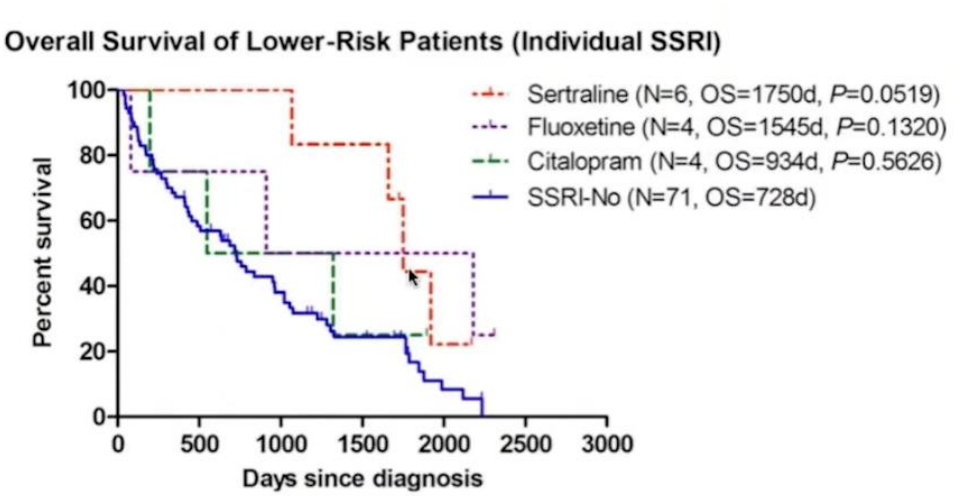
Lori Muffly,[1] Marcelo C. Pasquini,[2] Michael Martens,[3] Ruta Brazauskas,[2,3] Xiaochun Zhu,[2] Kehinde Adekola,[4] Mahmoud Aljurf,[5] Karen K. Ballen,[6] Ashish Bajel,[7] Frederic Baron,[8] Minoo Battiwalla,[9] Amer Beitinjaneh,[10] Jean-Yves Cahn,[11] Mathew Carabasi,[12] Yi-Bin Chen,[13] Saurabh Chhabra,[14] Stefan Ciurea,[15,16] Edward Copelan,[17] Anita D'Souza,[2] John Edwards,[18] James Foran,[19] Cesar O. Freytes,[20] Henry C. Fung,[21] Robert Peter Gale,[22] Sergio Giralt,[23] Shahrukh K. Hashmi,[24,25] Gerhard C. Hildebrandt,[26] Vincent Ho,[27] Ann Jakubowski,[23] Hillard Lazarus,[28] Marlise R. Luskin,[29] Rodrigo Martino,[30] Richard Maziarz,[31] Philip McCarthy,[32] Taiga Nishihori,[33] Rebecca Olin,[34] Richard F. Olsson,[35,36] Attaphol Pawarode,[37] Edward Peres,[38] Andrew R. Rezvani,[1] David Rizzieri,[39] Bipin N. Savani,[40] Harry C. Schouten,[41] Mitchell Sabloff,[42] Matthew Seftel,[43] Sachiko Seo,[44] Mohamed L. Sorror,[45,46] Jeff Szer,[47] Baldeep M. Wirk,[48] William A. Wood,[49] and Andrew Artz[50]

[12]

Current Clinical Trials for LR-MDS

- Vitamin C – theory it may enhance endogenous demethylation
- Sertraline

Significant Improvement in Overall Survival Among Patients Diagnosed with Low-Risk Myelodysplastic Syndrome (MDS) Treated with Selective-Serotonin-Reuptake-Inhibitors (SSRIs) - Baylor



Ang Li,Sarvari Venkata Yellapragada, MD,Martha Mims, MD,Gustavo A. Rivero, MD, Significant Improvement in Overall Survival Among Patients Diagnosed with Low-Risk Myelodysplastic Syndrome (MDS) Treated with Selective-Serotonin-Reuptake-Inhibitors (SSRIs), Blood, 2012, Fig 1.

Treatment for Higher Risk Patients

- Hypomethylating agents: azacitidine, decitabine
  - Can be used for both high risk and low risk patients
  - DO NOT increase survival in low risk patients (these treatments are only for symptomatic management when all else has failed)
    - Phase III trial of azacitidine in LR-MDS closed due to excess toxicity!
  - New oral azacitidine and decitabine recently approved
  - Response rates are 30-40% in high risk MDS patients by reducing the risk of transformation to AML and decreasing transfusion dependency

AZA-001 Trial

- The AZA-001 trial was a Phase III, international, multicenter, controlled, open-label trial of patients with high-risk MDS
- Pts randomly assigned treatment with azacitidine at 75 mg/m^2/day × 7 days every 28 days or conventional care (including best supportive care, low-dose cytarabine, or intensive chemotherapy)

In the AZA-001 trial in patients with higher risk-MDS or AML, compared with conventional care regimens, azacitidine prolonged OS and the time to AML transformation, improved 2-year survival rates and hematological response rates, and reduced RBC transfusion dependency

[13]

Table 1 Efficacy of azacitidine in pivotal multicentre, phase 3 trials in patients with MDS or AML

Study analysis	Treatment (no. of pts)	Overall haematological response[a] (% of pts)	Median OS (mo)	OS at 1 [32] or 2 years [31, 34, 35] (% of pts)	Median time to AML transformation (mo)
AZA-001 in pts (aged ≥18 years) with higher-risk MDS[b] or AML					
Primary analysis [31]	AZA[c] (179)	29***	24.5***,d,e	50.8***	17.8***
	Conventional care[f] (179)	12	15	26.2	11.5
Elderly pts aged ≥75 years [34]	AZA[c] (38)		NYR[e]	55**	
	Conventional care[f] (49)		10.8	15	
Pts with WHO-defined AML [35]	AZA[c] (55)		24.5*,e	50**	
	Conventional care[f] (58)		16	16	

How tolerable is Azacitidine?

- Most commonly, patients experienced neutropenia, anemia, or thrombocytopenia particularly during the first or two treatment cycles but then improvement with continued treatment
- Fever and worsened fatigue
- Constipation was the most frequently reported gastrointestinal event on AZA-001 (50.3%), and most occurrences were in the first two cycles of treatment and may have been exacerbated by antiemetic regimens.

[13]

Quality of Life Measurement in AZA-001

- quality of life was assessed by telephone interviews conducted at baseline and at 2 months, 3.5 months, and 6 months. Pts answered two standard surveys of quality of life
  - the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 and the Mental Health Inventory

- The data showed that patients treated with azacitidine demonstrated improved quality of life as compared with patients in the conventional care arm, with improvement in fatigue, dyspnea, physical functioning, and decreased psychological distress

[13]

Fun Fact: Elephants don’t really get cancer

- Researchers discovered that elephants have extra copies of cancer fighting genes, specifically *TP53!*

Take Away Points

References

1. Emmanuel C Besa, MD. *Myelodysplastic Syndrome (MDS) Workup: Approach Considerations, Complete Blood Count and Peripheral Blood Smear, Bone Marrow Studies*, Medscape, 2 Apr. 2021, emedicine.medscape.com/article/207347-workup.
2. "Types." *Aplastic Anemia & MDS International Foundation*, www.aamds.org/diseases/mds/types.
3. Key Statistics for Myelodysplastic Syndromes. American Cancer Society. Available at http://www.cancer.org/cancer/myelodysplasticsyndrome/detailedguide/myelodysplastic-syndromes-key-statistics. January 22, 2018; Accessed: January 26, 2021.
4. MD, Edward C. Klatt. *Hematopathology*, webpath.med.utah.edu/HEMEHTML/HEME012.html.
5. Shi, Z., Li, B., Huang, H., Qin, T., Xu, Z., Zhang, H., Fang, L., Pan, L., Hu, N., Qu, S., Huang, G., Gale, R.P. and Xiao, Z. (2019), Prognostic impact of red blood cell distribution width in myelodysplastic syndromes. Br J Haematol, 186: 352-355. https://doi.org/10.1111/bjh.15830
6. Endi Wang, MD, PhD, Elizabeth Boswell, MD, Imran Siddiqi, MD, PhD, Chuanyi Mark Lu, MD, Siby Sebastian, PhD, Catherine Rehder, PhD, Qin Huang, MD, PhD, Pseudo–Pelger-Huët Anomaly Induced by Medications: A Clinicopathologic Study in Comparison With Myelodysplastic Syndrome–Related Pseudo–Pelger-Huët Anomaly, *American Journal of Clinical Pathology*, Volume 135, Issue 2, February 2011, Pages 291–303, https://doi-org.proxy.hsl.ucdenver.edu/10.1309/AJCPVFY95MAOBKRS
7. Huff, Charlotte, et al. "MKSAP Quiz: Management after a Routine Exam." *ACP Internist*, 1 Apr. 2013, acpinternist.org/archives/2013/04/mksap.htm.
8. Tefferi A, Vardiman JW. Myelodysplastic syndromes. N Engl J Med. 2009;361:1872-1885.
9. Fenaux, Pierre, et al. "Luspatercept in Patients with Lower-Risk Myelodysplastic Syndromes." *New England Journal of Medicine*, vol. 382, no. 2, 2020, pp. 140–151., doi:10.1056/nejmoa1908892.
10. "Results from Phase III Study of REVLIMID® (Lenalidomide) Demonstrating Improved Transfusion Independence in Patients with Rare Blood Cancer, Non-Del-5Q Myelodysplastic Syndromes (MDS), Presented at ASH." *Investors Home*, ir.celgene.com/press-releases-archive/press-release-details/2014/Results-from-Phase-III-Study-of-REVLIMID-Lenalidomide-Demonstrating-Improved-Transfusion-Independence-in-Patients-with-Rare-Blood-Cancer-Non-Del-5Q-Myelodysplastic-Syndromes-MDS-Presented-at-ASH/default.aspx.
11. Parikh AR, Olnes MJ, Barrett AJ. Immunomodulatory treatment of myelodysplastic syndromes: antithymocyte globulin, cyclosporine, and alemtuzumab. *Semin Hematol*. 2012;49(4):304-311. doi:10.1053/j.seminhematol.2012.07.004
12. Muffly L, Pasquini MC, Martens M, Brazauskas R, Zhu X, Adekola K, Aljurf M, Ballen KK, Bajel A, Baron F, Battiwalla M, Beitinjaneh A, Cahn JY, Carabasi M, Chen YB, Chhabra S, Ciurea S, Copelan E, D'Souza A, Edwards J, Foran J, Freytes CO, Fung HC, Gale RP, Giralt S, Hashmi SK, Hildebrandt GC, Ho V, Jakubowski A, Lazarus H, Luskin MR, Martino R, Maziarz R, McCarthy P, Nishihori T, Olin R, Olsson RF, Pawarode A, Peres E, Rezvani AR, Rizzieri D, Savani BN, Schouten HC, Sabloff M, Seftel M, Seo S, Sorror ML, Szer J, Wirk BM, Wood WA, Artz A. Increasing use of allogeneic hematopoietic cell transplantation in patients aged 70 years and older in the United States. Blood. 2017 Aug 31;130(9):1156-1164. doi: 10.1182/blood-2017-03-772368. Epub 2017 Jul 3. PMID: 28674027; PMCID: PMC5580273.
13. Ritchie EK. Safety and efficacy of azacitidine in the treatment of elderly patients with myelodysplastic syndrome. *Clin Interv Aging*. 2012;7:165-173. doi:10.2147/CIA.S24659
14. Rifkin, Lucas H., MD, & Loo, Eric Y., MD. (2019). Molecular Genetics in Myelodysplasia Outcomes Prognostication. *Advances in Molecular Pathology, 2*(1), 35-43.